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Autocatalytic Oxidation of Ethers with Sodium Bromate

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Abstract—Sodium and potassium bromate are stable and easily stored oxidants. They can oxidize both open and cyclic ethers in aqueous solution at room temperature yielding esters and lactones. Kinetic studies of the oxidation of tetrahydrofuran to γ-butyrolactone indicate that the major active oxidation species is bromine and not bromate. The bromate is only a supporting agent, responsible for the initiation step and supplying bromine molecules by oxidizing bromide ions during the propagation step. In the oxidation of tetrahydrofuran, high yields of γ-butyrolactone were obtained. © 2000 Elsevier Science Ltd. All rights reserved.

Introduction

Sodium bromate and potassium bromate are commercially available, very stable solids which can be handled much more easily than liquid bromine or hypobromous acid solutions. Oxidation with bromates results in bromide ion formation, which can be safely treated or recycled. Thus such oxidations are recognized as friendly to the environment, compared to the traditional metal containing reagents such as chromate, permanganate, cerium and ruthenium salts etc.

In spite of much work, which has been performed on the oxidation of organic compounds with bromate, organic synthesis using bromate salts is still scanty. Overoxidation, bromination and oxidative bromination usually interfere with clean reactions and a host of products may result. Reaction conditions, particularly the strength and nature of the acid used are crucial, and determine in which direction the reaction proceeds.

Bromate salts can oxidize primary alcohols to aldehydes,[1–5,7] secondary alcohols to ketones[2,3,5,6] and under different sets of conditions the oxidation can result in formation of esters[2,3,5,7,8] and carboxylic acids.[4,8,10] Bromate salts were also shown to oxidize sulfides to sulfoxides,[9] hydroquinones and polyaromatics to quinones,[9,10] thiols to disulfides,[11] and iodobenzenes to iodoxybenzenes.[12] Even more interesting is the finding that reaction of dialkyl ethers, or cyclic ethers with sodium bromate in the presence of catalytic amounts of hydrobromic acid, gave esters or lactones in fairly good yields.[3] In addition it is known that bromine itself[13] and benzyl trimethyl ammonium tribromide[14] all induce the oxidative cleavage of ethers to carboxylic acids, ketones, esters and alcohols.

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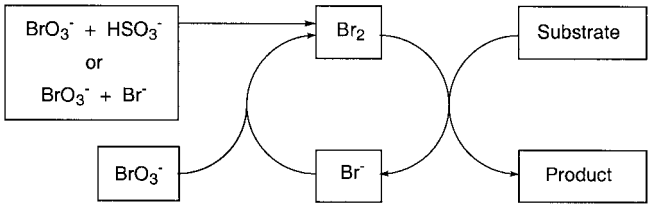
According to the literature, bromate itself cannot oxidize ethers. A ‘counter-reagent’ is needed, which can be of two types:

(a) A reducing agent, which reacts with the bromate in a redox type reaction to form bromine. The bromine formed then oxidizes the ether (Scheme 1). Examples of counter-reagents of this type are sodium bisulfite[15] or hydrobromic acid.[3]
Such a counter-reagent is needed only in catalytic amounts to initiate the reaction. Beyond this stage the oxidizing bromine can be supplied by the reaction



Scheme 1.

Keywords: oxidation of ethers; sodium bromate; lactones; esters; bromine.
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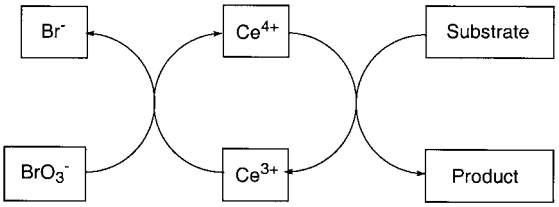
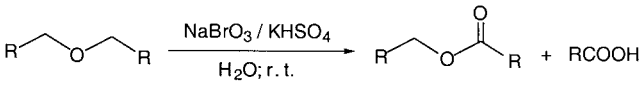


Scheme 2.



Scheme 3.

bromate–bromide, and the bromide anion becomes the counter-reagent.

(b) An oxidizing agent, which has the sole responsibility for the oxidation of the ether. The role of bromate in this case is to reoxidize the reduced form of the counter-reagent. Such a counter-reagent can be a cerium(IV) salt (Scheme 2).[16] In this case also only a catalytic amount of the counter-reagent is needed.

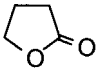
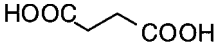
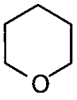
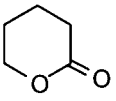
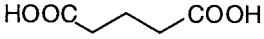
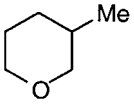
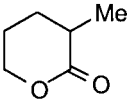
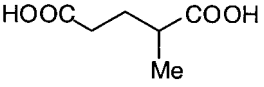
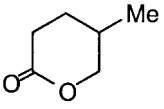
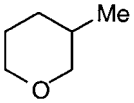
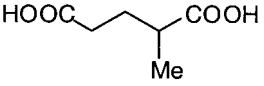
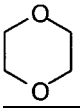
Results and Discussion

Oxidation of ethers with bromate salts only, without the addition of a counter-reagent was performed recently in our laboratory (Scheme 3), and the results obtained shed new light on the question of direct or indirect oxidation with bromates. The oxidations were performed in water at room temperature using equivalent quantities of sodium bromate and potassium hydrogen sulfate. An equivalent amount of dialkyl ether, or cyclic ether was added, which usually caused an exothermic reaction with coloration of the system (yellow). After total conversion of the ether (GC), the esteric or lactonic products were extracted into an organic solvent and evaluated either by isolation or by gas chromatography. Acidic products were isolated from the aqueous solution. All isolated products were characterized by comparison of their physical and spectral data with those of known samples.

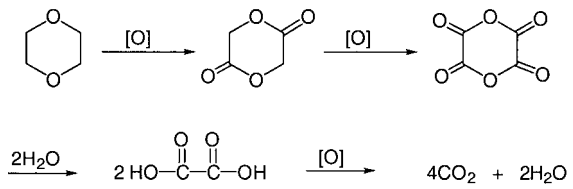
The results obtained with several ethers are summarized in Table 1. Under these conditions, diethyl ether was totally oxidized to acetic acid (98%) with just traces of ethyl acetate. Oxidation of the higher homologue, dibutyl ether, gave mainly butanoic acid (52%), accompanied by appreciable amounts (35%) of butyl butanoate.

The situation was different with cyclic ethers. Thus oxidation of tetrahydrofuran gave 80% of γ-butyrolactone and only 11% of succinic acid. Similarly, tetrahydropyran gave 69% of δ-valerolactone, and only 16% of glutaric acid. 3-Methyltetrahydropyran was oxidized with no selectivity; almost equal quantities (25 and 28%) of the α- and the γ-methyl-δ-valerolactones were obtained. An interesting degradation reaction took place upon oxidation of 1,4-dioxane. This cyclic diether was totally oxidized to carbon dioxide. The mechanism probably starts with oxidation to the bis-lactone, which is further oxidized to the bis-anhydride (Scheme 4). Decomposition in water yields 2 equiv. of oxalic acid, which are finally oxidized to carbon dioxide and water.

Table 1. Oxidation of alkyl ethers by sodium bromate in aqueous solution at room temperature

Ether	Time (h)	Ester	Yield (%)[a]	Acid	Yield(%)[a]
Et–O–Et	72	CH_3COOEt	Traces	CH_3COOH	98
Bu–O–Bu	48	$CH_3(CH_2)_2COOBu$	35[b]	$CH_3(CH_2)_2COOH$	52[b]
	16		80[c]		11
	20		69		16
	20		25[b]		Traces
			28[b]		
	120				87
	16			CO_2	Quantitative

[a] Isolated yield.
[b] The ratio between the products was determined by ^1H NMR.
[c] GC yield (isolated yield of lactone 73%).



Scheme 4.

Similar total oxidation with evolution of CO_2 was observed in the bromate oxidation reaction of mono- and disaccharides.

In order to optimize this oxidative process and to learn about its kinetics, we performed several sets of experiments using the oxidation of tetrahydrofuran (THF) to γ-butyrolactone (γ-BL), as a model reaction.

First, we studied the reaction as a function of the acidity of the medium by changing the concentration of $KHSO_4$ (see Fig. 1).

As can be seen, total conversion was obtained at a concentration of 0.6 M bisulfate, while the maximum yield of γ-BL (80%) was obtained using a 0.7 M concentration of the acid. Both lower acidities or higher acidities resulted in reduced yields of the lactone.

Fig. 2 represents the same reaction under different concentrations of sodium bromate. The total conversion of the 20 mmoles of THF, under these conditions needed 20 mmoles of bromate and the yield of γ-BL was 80%. Using higher concentrations of bromate lowered the yield of the lactone.

In a similar set of experiments, we studied the reaction as function of time (Fig. 3), using the optimal conditions as found in the two former sets of reactions, namely 20 mmol of THF, 20 mmol of sodium bromate in 0.7 M $KHSO_4$ solution. The results indicate maximum conversion after 16 h at room temperature with an 80% yield of γ-butyrolactone.

Upon analyzing the results, two facts deserve mention:

- Under the aforementioned set of conditions the yield of γ-BL is never quantitative, it increases gradually up to 80% and than starts to drop (see for example Fig. 3).
- At any point of the reaction coordinate the total quantities of THF (starting material) and γ-BL (product) are less than 100%.

These two facts are logical and can be explained if we recognize that the oxidation of THF by bromate is a multistep process which can proceed via several paths. Moreover the γ-BL itself under the reaction conditions can be further oxidized to succinic acid. The various optional oxidation

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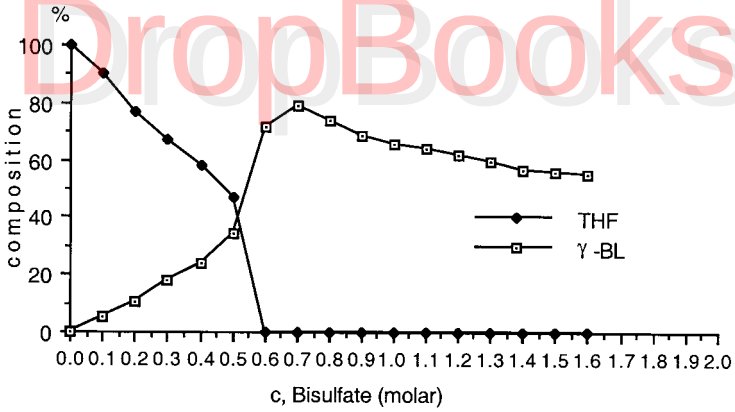


Figure 1. Conditions: 20 mmol THF; 20 mmol $NaBrO_3$; 25 mL aqueous solution of $KHSO_4$; room temperature 16 h; quantitative determination by GC analysis using 1,2-dichlorobenzene as the internal standard. The data in the figure represent an average of two different runs.

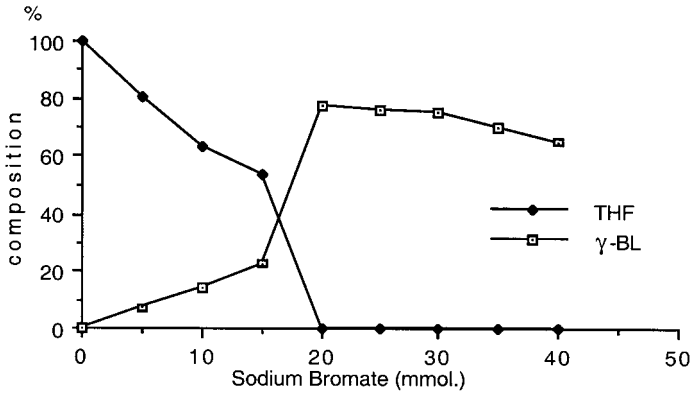


Figure 2. Conditions: 20 mmol THF; 25 mL of 0.7 M aqueous solution of $KHSO_4$; room temperature 16 h; quantitative determination as in Fig. 1.

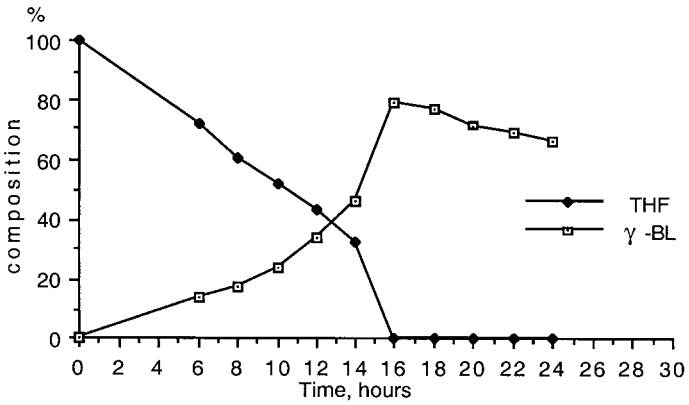


Figure 3. Conditions: 20 mmol THF; 20 mmol $NaBrO_3$; 25 mL of 0.7 M aqueous solution of $KHSO_4$; room temperature; quantitative determination as in Fig. 1.

paths are shown in Scheme 5. α-Hydroxylation of the ether (**1**) and formation of the hemiacetal (**2**) is the first step. The hemiacetal can now be directly oxidized to γ-BL (**5**), or be hydrolyzed to the open chain 4-hydroxybutanal (**3**). The hydroxy aldehyde is easily oxidized to the 4-hydroxybutanoic acid (**4**) which undergoes spontaneous cyclization to yield γ-BL (**5**). The γ-BL itself can undergo further oxidation to form lactone hemiacetal (**6**), succinic anhydride (**7**), and the final product, succinic acid (**8**).

This course of events explains why the yield of γ-BL is never quantitative (further oxidation of **5**), and it also explains why at any time during the reaction, the sum of THF and γ-BL do not reach 100% (presence of stable and semi-stable intermediates e.g. **2**, **3** and **4**).

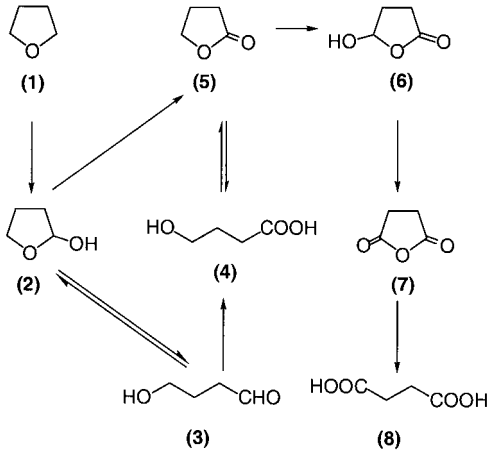
Two other observations need explanation:

- All the oxidative reactions are characterized by an initial slow phase, followed by a second phase, in which the reaction rate accelerates. The mass oxidation takes place in this second phase.
- During the oxidative reaction free bromine appears in the mixture. The appearance of the bromine coincides with the start of acceleration.

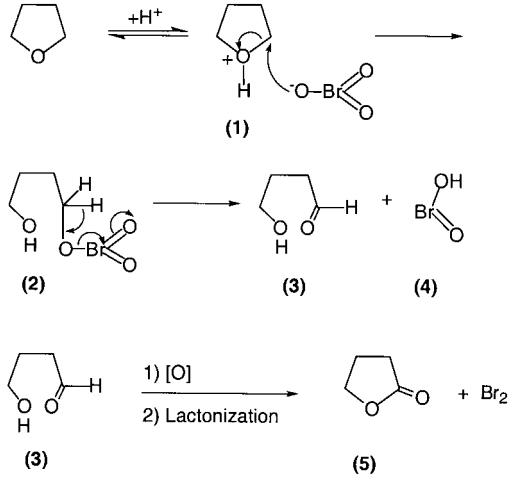
These two observations, namely bromine formation and reaction acceleration posed a question as to the nature of the active oxidant in this reaction. It is very well established that bromine can oxidize alicyclic and cyclic ethers and thus can convert THF to γ-BL.[13] At least two oxidizing species are present in our reaction mixture, the bromate and the bromine. Is it possible that two parallel mechanisms are active in this process? Or maybe the bromate is not oxidizing the ethers at all, and bromine, formed during the initial stage of the process, is the principal active agent?

We ran an extra few crucial experiments, in which we oxidized THF with bromate under the aforementioned optimized conditions, but with the addition of 1 equiv. of an alkene (e.g. cyclohexene). We reasoned that the alkene would act as a scavenger adding spontaneously any bromine formed. Indeed the yield of γ-BL, which without cyclohexene was ~80%, dropped dramatically to less than 5%, and most of the starting ether was recovered.

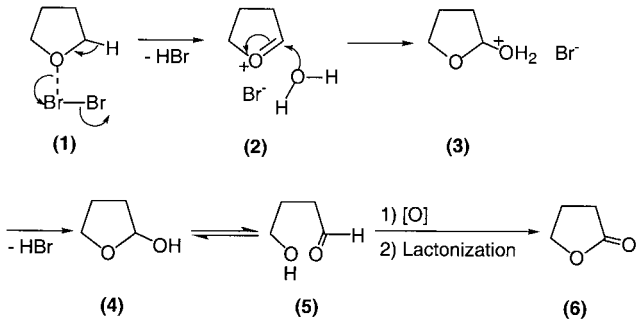
These three facts: (a) acceleration of the rate of reaction; (b) formation of Br_2; and (c) dramatic drop in oxidation, when Br_2 scavengers are present, suggest that two different mechanisms might be responsible for the oxidation of THF: (1) Oxidation by bromate itself, which seems to be a slow process; (2) Oxidation by bromine, which is a fast process.



Scheme 5. Oxidation paths of THF.



Scheme 6. Mechanism of THF oxidation by bromate.



Scheme 7. Mechanism of THF oxidation by bromine.

We suggest that under the aforementioned reaction conditions, the first mechanism is meaningful only in the initiation phase of the reaction, otherwise most of the oxidation proceeds via the second mechanism, namely, oxidation by bromine.

The oxidation of THF by bromate can be formulated as in Scheme 6.

The protonated ether (**1**) undergoes substitution with bromate at the activated α-carbon to yield a bromate ester (**2**). Elimination of bromite (**4**) yields the α-hydroxy aldehyde (**3**) which undergoes further oxidation to the γ-hydroxy acid, concurrently with formation of bromine. The γ-hydroxy acid cyclizes to the γ-BL (**5**).

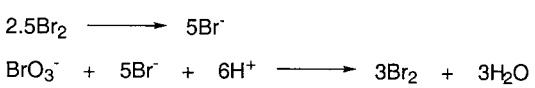
This is a slow mechanism representing only the initiation step of the oxidation process. Its importance is in the formation of bromine, which is a faster oxidizer of ethers. Beyond this initiating step the bromate becomes only a reservoir supplying molecular bromine.

The mechanism of THF oxidation by bromine can be formulated as in Scheme 7.

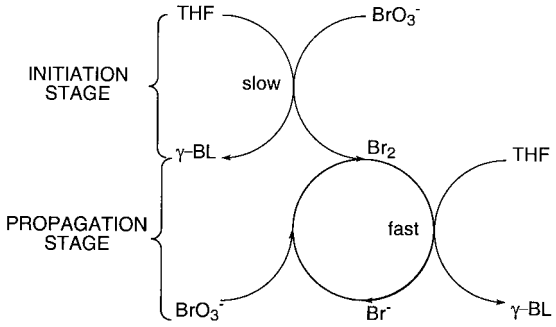
Charge transfer complexation of bromine with THF (1)[13] facilitates elimination of HBr to yield the intermediary oxonium salt (**2**). Addition of a molecule of water and elimination of a second molecule of HBr gives the hemiacetal (**4**). The hemiacetal is in equilibrium with the open-chain γ-hydroxy aldehyde (**5**), which can undergo a second oxidation followed by cyclization to the γ-BL (**6**). The possibility of direct oxidation of the hemiacetal (**4**) to γ-BL (**6**) is not excluded.

The fact that the rate of oxidation accelerates during the process, strengthens our assumption that oxidation with bromine is the main operating mechanism. When bromine oxidizes THF, bromide is formed. Bromate can react with the bromide in the acidic medium to yield bromine (Scheme 8).

If we assume that 2.5 molecules of Br_2 react with THF



Scheme 8.



Scheme 9. General process of THF oxidation by bromate.

according to Scheme 7 to yield five bromide ions, these ions will then react with one molecule of bromate to produce three molecules of bromine. Thus, in this cyclic process in which we start with 2.5 and produce three molecules, which can now further oxidize the ether, we gain half a molecule of Br_2. In each oxidative cycle we produce an extra half a molecule of bromine and the result is acceleration of the oxidation reaction. This is a typical autocatalytic process.

We suggest the following general scheme (Scheme 9) to describe the oxidation process of ethers with bromate salts: a slow initiation process, in which Br_2 is formed followed by an accelerated propagation process.

In conclusion, our data on direct oxidation of ethers with bromate point towards bromine as the main active oxidant. Bromate itself is responsible only for the initiation step and than plays the role of a co-oxidizer or bromine supplier.

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Experimental

All starting materials were commercially available. GC analysis was performed on a Perkin–Elmer 8310 chromatograph with a flame ionization detector (FID) fitted with a 2×1000 mm column, packed with 10% Carbowax in Chromosorb. The yields of products were determinated by isolation using distillation techniques and from the peak area based on internal standart GC technique. The internal standart used was 1,2-dichlorobenzene. ^{1}H NMR spectra were recorded on a Bruker DPX-200 spectrometer.

General procedures for oxidation of ethers with sodium bromate

To a stirred mixture of ether and water (0.1 mol ether and 100 mL of water) were added 15.1 g (0.1 mol) of sodium bromate and 13.6 g (0.1 mol) of potassium hydrogen sulfate. Both cooling of the reaction mixture and an efficient reflux condenser were used in order to minimize evaporation of the ether and keeping the reaction temperature in the range 25–30°C. Stirring was continued at room temperature for 16–20 h. To quench any excess of bromine formed, acidic sodium sulfite solution was used. Thus, 10% aqueous solution of sodium sulfite (about 140–150 mL) and 13.6 g (0.1 mol) of potassium hydrogen sulfate were added. The mixture was cooled and extracted with CH_2Cl_2 (5×30 mL in the case of lactone formation, or 3×30 mL in the case of

linear esters). The combined organic layer was dried over magnesium sulfate, the solvent removed in vacuum and the residue purified by distillation. γ-Butyrolactone was distilled at 204–205°C/760 mm. Yield: 6.3 g (73%). δ-Valerolactone was distilled under reduced pressure at 97–98°C/10 mm. Yield: 6.9 g (69%). The mixture of α-methyl-δ-valerolactone and γ-methyl-δ-valerolactone was distilled under reduced pressure at 97–101°C/10 mm. Yield: 6.4 g (53%). ^{1}H NMR analysis showed the presence of both products in ratio of 25% and 28% respectively (ratio of α-methyl doublet at 1.18 ppm and γ-methyl doublet at 1.02 ppm). Dibutyl ether oxidation products were distilled at 160–165°C. Yield: 13.7 g (87%). ^{1}H NMR analysis showed the presence of butyl butanoate and butyric acid in 2:3 ratio (ratio of the etheric methylene triplet at 4.07 ppm and the α-methylene triplet of the acid at 2.34 ppm). Thus the yields are 35 and 52%, respectively.

Quantitative determinations (Figs. 1–3)

2 mL of the reaction mixture were mixed with 5 mL of 0.032 M 1,2-dichlorobenzene solution in toluene. This heterogeneous mixture was dried over anhydrous sodium sulfate until a clear solution was obtained. A 0.5 μL sample of the toluene solution was injected. Usually this procedure was repeated twice. Calibration curves were drawn for both starting material and product.

Acknowledgements

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References

1. Farkas, L.; Perlmutter, B.; Schachter, O. *J. Am. Chem. Soc.* **1949**, *71*, 2833.
2. Farkas, L.; Schachter, O. *J. Am. Chem. Soc.* **1949**, *71*, 2827.
3. Kajigaeshi, S.; Nakagawa, T.; Nagasaki, N.; Yamasaki, H.; Fujisaki, S. *Bull. Chem. Soc. Jpn* **1986**, *59*, 747.
4. Behr, A.; Eusterwiemann, K. *J. Organomet. Chem.* **1991**, *403*, 209.
5. Tomioka, H.; Oshima, K.; Nozaki, H. *Tetrahedron Lett.* **1982**, *23* (5), 539.
6. Yamamoto, Y.; Suzuki, H.; Moro-oka, Y. *Tetrahedron Lett.* **1985**, *26* (17), 2107.
7. Kanemoto, S.; Tomioka, H.; Oshima, K.; Nozaki, H. *Bull. Chem. Soc. Jpn* **1986**, *59*, 105.
8. Takase, K.; Masuda, H.; Kai, O.; Nishiyama, Y.; Sakaguchi, S.; Ishii, Y. *Chem. Lett.* **1995**, 871.
9. Ho, T.-L. *Synth. Commun.* **1979**, *9* (4), 237.
10. Banerjee, A.; Dutt, S.; Sengupta, D.; Adak, M. M.; Samaddar, H. *J. Ind. Chem. Soc.* **1983**, *60* (3), 275.
11. Adak, M. M.; Banerjee, G. C.; Banerjee, A. *J. Ind. Chem. Soc.* **1985**, *62* (3), 224.
12. Banerjee, A.; Banerjee, G. C.; Bhattacharya, S.; Banerjee, S.; Samaddar, H. *J. Ind. Chem. Soc.* **1981**, *58* (6), 605.
13. Deno, N. C.; Potter, N. H. *J. Am. Chem. Soc.* **1967**, *89*, 3550.
14. Kajigaeshi, S.; Kawamukai, H.; Fujisaki, S. *Bull. Chem. Soc. Jpn* **1989**, *62*, 2585.
15. Sakaguchi, S.; Kikuchi, D.; Ishii, Y. *Bull. Chem. Soc. Jpn* **1997**, *70*, 2561.
16. Olah, G. A.; Gupta, B. G. B.; Fung, A. P. *Synthesis* **1980**, 897.